Red Meat Intake and Risk of Leukemia: A Protocol of Systematic Review and Meta-Analysis

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Abstract

Background: The intricate interplay of risk factors and their modifying effects on health outcomes, known as effect modification, remains a critical and complex phenomenon in epidemiological research. In this study, we rigorously explore the dimensions of effect modification, focusing on its quantification, qualitative and quantitative manifestations, and implications for both research and practice. Drawing on a comprehensive analysis of existing literature, we examine the challenges and opportunities in identifying and understanding these interactions among variables. **Methods:** This investigation adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, employing a meticulous search strategy to identify relevant studies from electronic databases. Studies exploring the association between red meat intake and the risk of leukemia are meticulously selected, with data extraction encompassing study characteristics, exposure assessment methods, outcome evaluation, and adjusted effect estimates. **Results:** The synthesis of the selected studies is conducted using random-effects meta-analysis to estimate the pooled effect size of red meat intake on leukemia risk. Subgroup analyses dissect potential sources of heterogeneity, accounting for variations in study design, population characteristics, and geographic location. Sensitivity analyses assess the robustness of the results, scrutinizing the influence of individual studies on the overall effect estimate. A dose-response analysis examines potential trends in the relationship between different levels of red meat consumption and leukemia risk. **Conclusion:** Through a systematic review and meta-analysis augmented by the GRADE assessment, this study aims to contribute rigorous evidence on the relationship between red meat intake and leukemia risk. By quantifying the effect size, exploring sources of heterogeneity, and integrating GRADE, we endeavor to offer a comprehensive evaluation that informs future research directions and underscores the potential impact on public health recommendations.

Keywords: Red Meat Intake - Leukemia Risk

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Introduction

1.1 Background

Globally, leukemia, a malignant tumor that affects tissues that produce blood, is a major health concern. It has a significant morbidity and mortality rate and is defined by the aberrant growth of immature blood cells. Leukemia has a complicated etiology that is influenced by a complex interplay of genetic, environmental, and lifestyle variables [1-3].

Leukemia and other cancers have both been linked to dietary habits for a long time. Red meat consumption has drawn the most attention among the other dietary components because of its conceivable link to a number of cancers. High-quality protein and necessary elements can be found in red meat, which includes beef, hog, lamb, and processed meat products. However, it also contains substances that might be carcinogenic, such as nitrosamines, polycyclic aromatic hydrocarbons, and heterocyclic amines [4-13].

Red meat consumption has been linked to a number of diseases, including colorectal cancer, however, the link between red meat consumption and the risk of leukemia has not been well explored. While some studies have found no conclusive correlation, some have claimed a positive correlation, attributing it to the possible carcinogens included in red meat. Therefore, a thorough and methodical analysis of the available data is necessary to clarify any possible associations between the consumption of red meat and the risk of developing leukemia [6, 14-19].

We suggest a systematic study and meta-analysis to look at the connection between red meat consumption and the risk of leukemia in order to fill this knowledge vacuum. This study seeks to give a thorough and evidence-based assessment of the association, evaluate the quality of the existing evidence, and identify potential sources of heterogeneity by synthesizing and assessing the existing literature.

The results of this study will carry significant implications for public health guidance concerning red meat consumption and its potential impact on leukemia prevention. Gaining a better understanding of the relationship between red meat intake and the risk of developing leukemia could provide valuable insights for shaping dietary recommendations. It has the potential to inform individuals about possible lifestyle adjustments that may help reduce their susceptibility to this type of blood cancer.

1.2 Rationale

This systematic review and meta-analysis aim to investigate the relationship between red meat intake and the risk of leukemia. By synthesizing the available evidence, we aim to address the existing knowledge gaps, provide a comprehensive assessment of the association, and guide future research and public health recommendations.

1.3 Objectives

The specific objectives of this study are as follows:

- To systematically review and identify relevant studies investigating the association between red meat intake and leukemia risk.
- To assess the quality and risk of bias of included studies.
- To conduct a meta-analysis to quantify the overall effect size of red meat intake on leukemia risk.
- To explore potential sources of heterogeneity among studies.
- To assess publication bias and consider its impact on the findings.
- To discuss the implications of the findings and provide recommendations for future research and public health guidelines.

Methods

This study followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocol [20] to conduct systematic reviews and meta-analyses in a meticulous manner. To assess the quality of evidence, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool will be employed. GRADE offers a comprehensive framework to evaluate the certainty of evidence across studies and facilitates the translation of findings into actionable recommendations [21].

2.1 Search Strategy

A comprehensive literature search will be conducted in electronic databases (e.g., PubMed, Web of Science, and Scopus) to identify relevant studies published from the inception of the databases up to the present. The search strategy will include a combination of keywords and controlled vocabulary related to red meat intake, leukemia, and epidemiological study designs. The reference lists of relevant articles and review papers will also be scanned for additional studies.

Leukemia

Blood cancer, Leukemic diseases, Hematological malignancies, Acute lymphoblastic leukemia, Acute myeloid leukemia, Chronic lymphocytic leukemia, Chronic myeloid leukemia.

Red meat intake

Red meat consumption, Meat consumption, Meat intake, Dietary intake of red meat Consumption of beef, pork, lamb, Intake of processed meat.

PubMed

("red meat"[MeSH Terms] OR (("red meat consumption"[Title/Abstract] OR "meat consumption"[Title/Abstract] OR "meat intake"[Title/Abstract] OR ("eating"[MeSH Terms] OR "eating"[All Fields] OR ("dietary"[All Fields] AND "intake"[All Fields]) OR "dietary intake"[All Fields])) AND "red meat"[Title/Abstract]) OR (("intake"[All Fields] OR "intake s"[All Fields] OR "intakes"[All Fields] OR "intake

s"[All Fields] OR ("intake"[All Fields] OR "intake s"[All Fields] OR "intakes"[All Fields])) AND "processed meat"[Title/Abstract]) OR "meat"[Title/Abstract]) AND ("leukemia"[MeSH Terms] OR ("blood cancer"[Title/Abstract] OR "leukemic diseases"[Title/Abstract] OR "hematological malignancies"[Title/Abstract] OR "acute lymphoblastic leukemia"[Title/Abstract] OR "acute myeloid leukemia"[Title/Abstract] OR "chronic lymphocytic leukemia"[Title/Abstract] OR "chronic myeloid leukemia"[Title/Abstract])).

Scopus

(TITLE-ABS-KEY ("meat" OR "red AND meat" OR "red AND meat AND consumption" OR "meat AND consumption" OR "meat AND intake" OR "processed AND meat") AND TITLE-ABS-KEY ("blood AND cancer" OR "hematological AND malignancies" OR "acute AND lymphoblastic AND leukemia" OR "acute AND myeloid AND leukemia" OR "chronic AND lymphocytic AND leukemia" OR "chronic AND myeloid AND leukemia" OR "leukemia")).

Web of Science

meat OR red meat OR red meat consumption OR meat intake OR processed meat (Topic) AND blood cancer OR hematological malignancies OR acute lymphoblastic leukemia OR acute myeloid leukemia OR chronic lymphocytic leukemia OR chronic myeloid leukemia OR leukemia (Topic).

2.2 Study Selection

The inclusion criteria for study selection will be defined as follows:

- Study Design: Observational studies (cohort, case-control) reporting on the association between red meat intake and leukemia risk.

- Participants: Studies involving human populations of any age or gender.

- Exposure: Red meat consumption assessed through dietary assessment methods (e.g., food frequency questionnaires, dietary records).

- Outcome: Leukemia diagnosis confirmed by established diagnostic criteria.

- Language: Studies published in English.

Two independent reviewers will screen the titles, abstracts, and full texts of identified studies for eligibility. Any discrepancies will be resolved through discussion or by involving a third reviewer if necessary.

2.3 Data Extraction

A standardized data extraction form will be developed to collect relevant information from the included studies. The following data will be extracted:

- Study characteristics: Author, year of publication, country, study design, sample size.

- Participant characteristics: Age, gender distribution, population characteristics (e.g., general population, specific age groups).

- Exposure assessment: Methods used to assess red meat intake, exposure categories, dose-response

information.

- Outcome assessment: Leukemia subtype(s), diagnostic criteria, follow-up duration.

- Adjusted effect estimates: Risk ratios, odds ratios, hazard ratios, with corresponding 95% confidence intervals.

- Covariates adjusted for in the analyses.

- Funding source and potential conflicts of interest.

2.4 Quality Assessment

The quality and risk of bias of included studies will be independently assessed by two reviewers using established tools, such as the Newcastle-Ottawa Scale for cohort and case-control studies. Assessment will cover study design, participant selection, exposure and outcome assessment, confounding control, and statistical analysis. Any disagreements will be resolved through discussion or by involving a third reviewer.

2.5 Data Synthesis

The synthesis of data will be a pivotal step in this systematic review and meta-analysis, aimed at deriving a comprehensive understanding of the association between red meat intake and leukemia risk. The process involves quantifying the effect size through meta-analysis and exploring sources of heterogeneity to unravel the nuances that contribute to variability among study results.

2.5.1 Meta-Analysis of Effect Size

If a sufficient number of studies meeting the inclusion criteria are identified, a meta-analysis will be conducted to estimate the pooled effect size of red meat intake on leukemia risk. The random-effects model will be employed to account for inherent heterogeneity across studies. The pooling of effect sizes will generate an overall estimate of the association between red meat consumption and leukemia risk, providing a quantitative measure of the relationship.

2.5.2 Subgroup Analyses

Subgroup analyses will be performed to examine potential sources of heterogeneity that may contribute to variations in study outcomes. Subgroups will be defined based on study design, population characteristics (e.g., age, gender), geographic location, and assessment methods for red meat intake. These analyses will offer insights into whether certain factors modify the effect estimate and provide a deeper understanding of potential effect modifiers.

2.5.3 Sensitivity Analyses

Sensitivity analyses will be conducted to assess the robustness of the meta-analysis findings. These analyses involve systematically evaluating the impact of individual studies on the overall results. Studies with a high risk of bias or studies that contribute disproportionately to heterogeneity will be temporarily excluded to evaluate whether their inclusion significantly influences the pooled effect size. This exploration of the impact of specific studies on the overall estimate enhances the reliability of

the meta-analysis.

2.5.4 Dose-Response Analysis

If a sufficient number of studies provide dose-response data, a dose-response analysis will be performed to examine potential trends in the association between different levels of red meat intake and leukemia risk. This analysis can provide valuable insights into the potential dose-dependent relationship, helping to further elucidate the nature of the association.

2.5.5 Exploration of Heterogeneity

The heterogeneity among study results will be explored using statistical methods and subgroup analyses. The I^2 statistic will be calculated to quantify the proportion of total variation across studies that is attributable to heterogeneity rather than chance. Subgroup analyses will aim to identify potential effect modifiers and sources of variability, such as study characteristics, population characteristics, and geographic location.

2.5.6 GRADE Assessment Integration

The results of the data synthesis will be integrated with the GRADE assessment to provide a comprehensive evaluation of the quality of evidence and the strength of the association between red meat intake and leukemia risk. The GRADE assessment's consideration of risk of bias, inconsistency, indirectness, imprecision, and publication bias will contribute to a holistic understanding of the overall certainty of evidence.

2.5.7 Forest Plots

The results of individual studies and the pooled effect size will be visually presented using forest plots. These plots provide a graphical representation of the effect estimates, along with their confidence intervals, for each study included in the meta-analysis. Forest plots offer a clear visualization of the variability and overall trend of the association, aiding in the interpretation of the results.

2.5.8 Reporting of Results

The results of the meta-analysis, subgroup analyses, sensitivity analyses, and dose-response analysis will be thoroughly reported. Effect sizes, confidence intervals, statistical significance, and heterogeneity statistics will be presented in a clear and organized manner. The synthesis of data will be accompanied by thoughtful interpretations, relating the findings back to the research objectives and the broader context of leukemia risk and dietary habits.

By rigorously conducting meta-analyses, subgroup analyses, and sensitivity analyses while integrating the GRADE assessment, this systematic review ensures a comprehensive evaluation of the association between red meat intake and leukemia risk. The synthesis of data and consideration of heterogeneity contribute to a nuanced understanding of the complex relationship, fostering evidence-based conclusions that inform future research directions and public health guidelines.

2.6 Publication Bias

Publication bias will be assessed using funnel plots and statistical tests, such as Egger's regression test or Begg's rank correlation test. If publication bias is detected, appropriate measures, such as trim-and-fill analysis or the Duval and Tweedie trim-and-fill method, will be used to adjust the effect estimates accordingly.

2.7 Ethics Considerations

Since this study involves the analysis of published data, ethical approval is not required. However, adherence to ethical guidelines, such as the PRISMA statement, will be ensured.

Results

3.1 Study Selection Flow

A flow diagram will be provided to illustrate the study selection process, including the number of studies identified, screened, assessed for eligibility, and included in the analysis.

3.2 Descriptive Analysis

The characteristics of the included studies will be summarized, including study design, sample size, participant characteristics, exposure and outcome assessment methods, and key findings.

3.3 Quantitative Analysis

The results of the meta-analysis will be presented, including the pooled effect size (e.g., risk ratio, odds ratio) and corresponding 95% confidence interval. Forest plots will be used to visualize the effect estimates of individual studies and the overall pooled effect.

3.4 Sensitivity Analysis

Sensitivity analyses will be conducted to assess the influence of different methodological choices or the exclusion of studies with a high risk of bias on the overall findings. The results of sensitivity analyses will be reported and discussed.

3.5 Publication Bias Assessment

The results of publication bias assessment using funnel plots and statistical tests will be presented and discussed. If publication bias is detected, adjusted effect estimates using appropriate methods will be reported.

Discussion

4.1 Summary of Findings

The main findings of the systematic review and meta-analysis will be summarized, emphasizing the overall effect size of red meat intake on leukemia risk and the level of statistical significance.

4.2 Interpretation

The implications of the findings will be discussed in the context of the existing literature. Possible biological mechanisms underlying the association between red

meat intake and leukemia risk will be explored. Any inconsistencies or discrepancies among included studies will be analyzed and explained. Limitations of the study, such as heterogeneity, biases, or limitations of the available evidence, will be acknowledged.

4.3 Strengths and Limitations

The strengths and limitations of the study design, methodology, and data sources will be critically evaluated. The quality and risk of bias of included studies will be discussed, along with potential sources of heterogeneity and publication bias.

4.4 Future Research

Based on the findings and identified knowledge gaps, recommendations for future research will be provided. Suggestions for improving study design, addressing limitations, exploring specific subgroups, or investigating potential confounders will be discussed.

In conclusion, A concise summary of the key findings will be provided, emphasizing the implications of the study for understanding the association between red meat intake and leukemia risk. Recommendations for public health guidelines and future research directions will be presented.

Acknowledgments

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